*Novelty:*

<u>The Rejection of Claims 1, 2, 8, 9, 11, 12, 17,18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92, 102, and 103 Under 35 U.S.C. §102(b)</u>

The rejection of claims 1, 2, 8, 9, 11, 12, 17,18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92, 102, and 103 under 35 U.S.C. §102(b) is maintained, the U.S. Patent and Trademark Office finding the distinctions drawn by applicants as "mere sophistry." The U.S. Patent and Trademark Office suggests that arguing over the meaning of a single word will not make the current claims allowable. In addition, the U.S. Patent and Trademark Office asserts that no evidence has been provided that "relaxed toroids" are indeed different from "rods." However, evidence has been provided that demonstrates that the compositions taught by Hanson (U.S. 5,844,107) do not meet all the limitations of the claims.

The claims require the following physical properties in a subset of complexes in a composition:

- Rod-shaped
- Diameter of 10-20 nm
- Condensed
- Single nucleic acid molecule.

Hanson does not teach a single type of complex that has all of these properties. Even if one were to accept the postulate of the U.S. Patent and Trademark Office that the recited rod-shaped complexes and Hanson's rod-like toroids[1] are really the same shape, the result would not be the complexes with the recited properties. Hanson's rod-like toroid complexes are relaxed, which Hanson himself uses as a descriptor different from and ***in contrast*** to "condensed." ("For the purpose of the present invention, it is helpful to characterize DNA as having one of the following states: normal (uncondensed); condensed; relaxed; uni-aggregated (clusters of unimolecular toroids); multi-aggregated

[1] Hanson Table 104, footnote 2: "the structure resulting from the condensation are rod-like relaxed toroids of increased size (Relaxed)."

(clusters of multimolecular toroids); and precipitated. These states are defined in terms of their appearance under electron microscopy (see Table 103).") Hanson at column 19, lines 52-59. The recited complexes of the present claims are condensed. Hanson teaches that its "rod-like relaxed" toroid complexes are ***not*** condensed. This is intrinsic evidence that Hanson does not anticipate the claimed invention.

Hanson explains the difference between relaxed and condensed DNA on the basis of solvation. "Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is in the form of isolated spheres or toroids. It is not fibrous to an appreciable degree. Relaxed DNA, typically formed by dissociation of polycation from the DNA, forms fibers." Col. 19, lines 60-64. Hanson describes the relaxed toroids observed in Fig. 1F, further providing distinctions between the claimed and prior art structures: "In Fig. 1F, we see a DNA complex, at a concentration of 1.068M NaCl, which is above optimal for condensation of this complex. The DNA is in the relaxed state. Note the branched unimolecular toroids in which a nucleus of condensation is visible and the rod-like DNA fibers." Col. 6, lines 11-16.

The U.S. Patent and Trademark Office provides a post-filing date article by Martin et al. to demonstrate that the rod-like relaxed toroids of Hanson spontaneously interconvert with the recited condensed rods. Martin is cited as teaching that the "ring and rod-like structures exist dynamically, having the ability to reversibly equilibrate between structures." However, the use of Martin is inapposite. Martin teaches that its toroidal and rod-like structures are not actually condensed. Rather they appear to be an intermediate in the process. Martin calls these "an early stage of condensate formation." Page 111, col. 1, third full paragraph. Moreover, the reversible shape conversion directly contradicts an express teaching in the subject application. The specification clearly teaches that the condensed, unimolecular, rod-shaped complexes of the present invention are shape-stable. "Interestingly, it has been found that once a particle has been compacted into a particular shaped particle, removal and replacement of the counterion, such as by dialysis, does not significantly alter the shape once assumed. Thus a favorable shape can be obtained with a particle using a non-optimum counterion for physiological purposes and the counterion can be replaced with a superior counterion, while retaining the shape obtained during compaction with the original counterion." Page 14, first

paragraph. Thus, if the claimed complexes do not change morphology upon dialysis with a different counterion, certainly they will not spontaneously change morphology in solution as do Martin's. This is intrinsic evidence that the teachings of Martin as applied to Hanson are inapposite to the recited complexes.

Moreover, the U.S. Patent and Trademark Office urges that it is impossible to have a pure population of either toroids or rods when DNA is condensed as by Hanson or the instant specification. Office Action at page 4, lines 9-11. The claims, however, do not require a pure preparation. The claims require only a subset of complexes which are rod-shaped, condensed, and have a diameter of 10-20 nm. Hanson does not teach a composition containing such a subset. Hanson does not describe such a subset. Such a subset is not inherently present by virtue of the asserted Martin phenomenon, since Martin requires a fluidity of shape which is not displayed by the recited complexes.

The recited subset of complexes is not necessarily and inherently present in Hanson's preparations because Hanson did not practice the same method of production as applicants. Hanson did not use acetate as a counterion of the polycation. Hanson mentions acetate in a number of contexts, none of which is as the counterion of the polycation used for complex formation. Hanson teaches acetate in the uranyl acetate stain for electron microscopy, in an additive to reverse precipitation or aggregation of complexes, in a precipitating agent for DNA, in a stain for cells, and in a reaction mixture to make antibody fragments. But Hanson does not teach using acetate as the counterion for the polycation with which DNA condensation is performed.

Applicants have pointed to intrinsic evidence within the documents themselves that indicate that Hanson does not teach the same physical entity as claimed. Intrinsic evidence within the teachings of the involved documents is indeed evidence and does not constitute mere argument.

The office action concludes that "[w]ithout a doubt, Hanson et al. anticipate every limitation regarding the nature of polycation molecules, counterions, and DNA condensation." This is plainly not true. The difference between Hanson and the claimed invention, is not simply a difference in description of two identical compositions. Hanson is made with different counterions. Hanson forms a different composition. Hanson describes its composition differently. The U.S. Patent and Trademark Office must

consider all the relevant facts and cannot simply ignore differences. All the characteristics of the recited complexes must be found the prior art teaching.

Hanson does not anticipate the subject matter of claims 1, 2, 8, 9, 11, 12, 17, 18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92, 102, and 103. Withdrawal of this rejection is respectfully requested.

***Obviousness:***

The Rejection of Claims 3, 10, 19, 31, 35, 51-53, 63-65, 67,68, 76-78, and 104 Under 35 U.S.C. §103(a) over Hanson, Park, and Schacht

The Rejection of Claims 58-62, 66, 73-75, 79-82, and 122 Under 35 U.S.C. §103(a) over Hanson, Park, and Mao

The Rejection of Claims 4-7, 13-16, 39-42, 54-57, 69-72, 106-109, 114-117 Under 35 U.S.C. §103(a) over Hanson, Park, Schacht, and Kwoh

As detailed above, Hanson does not teach a composition comprising complexes that are rod-shaped when visualized by transmission electron microscopy, wherein the rod-shaped complexes have a diameter of 10-20 nm when visualized by transmission electron microscopy, wherein the nucleic acid molecules of the rod-shaped complexes are condensed, wherein the complexes are colloidally stable in normal saline. None of the secondary references teaches how to obtain such complexes.

Park is cited for teaching the use of PEG on polylysine attached through an amino terminal linkage.

Schacht is cited for teaching a disulfide linkage via a cysteine moiety of polylysine to PEG.

Mao is cited for teaching the lyophilization of complexes and administration to cells.

Kwoh is cited by the U.S. Patent and Trademark Office for teaching that polylysines of all sizes condense plasmid DNA into toroids and rod-shaped structures as shown by electron microscopy ranging in size from 40 to 80 nm for rods. Further, Kwoh is cited by the U.S. Patent and Trademark Office for teaching that PEG conjugation to PLL-DNA makes longer rods and more rods and that size can be measured using electron

microscopy. Even so, Kwoh does not teach remaining elements of the claims. Kwoh's complexes are not colloidally stabile in normal saline.

Kwoh teaches the instability of her complexes in a number of different ways. In Table 1, Kwoh compares the size of her polylysine complexes (PLL10K and PLL26K) in water to the size in 0.15 M NaCl. The complexes aggregate in the saline, increasing particle size by 5-fold. See also Fig.3A, where the complexes in NaCl have larger diameters at all charge ratios. Similarly, Kwoh teaches that PEG-lysine complexes are not colloidally stable in physiological saline. Complexes made with DNA and PLL10K-PEG5K have a diameter of 80.5 nm in water, which increases to 187 nm in saline (see page 185, column 1, lines 12 to column 2, line 3.)

There is no teaching or suggestion that using any particular elements of the secondary reference teachings combined with Hanson's teaching would result in the recited rod-shaped complexes. Nonetheless, the U.S. Patent and Trademark Office urge that the claimed compositions are not "anything more than what has been known in the art." The examiner finds "the compositions of the instant claims to be obvious variants of what has been performed by others skilled in the art."

How are the compositions which are claimed better than Hanson's?
As detailed above, Hanson's rod-like particles are relaxed. Such complexes are more susceptible to degradation in nuclease-rich environments, such as serum. In such environments, the complexes of the present invention are more stable. As shown in Figure 18 of the application, poorly condensed DNA is more susceptible to nuclease degradation. How are the compositions which are claimed better than Kwoh's? The compositions of the present invention are stable in normal saline.[2] This, too, is an important characteristic for use in the human body.

[2]As recited in claims 1, 8, 17, 26, and 28 : "wherein the complexes are colloidally stable in normal saline."

Withdrawal of the rejection is respectfully requested because the cited art fails to present a *prima facie* case of obviousness.

Respectfully submitted,

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